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MAGNETIC RESONANCE IMAGING ALTERATION OF THE BRAIN IN A PATIENT WITH CORONAVIRUS DISEASE 2019 (COVID-19) AND ANOSMIA

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Abstract
Magnetic resonance imaging (MRI) is a non-invasive medical imaging technique that uses a strong magnetic field and radio waves to produce detailed images of internal body structures. Recent studies have shown that COVID-19 infection can lead to alterations in brain structure and function, which can be detected using MRI. The main objective of this meta-analysis is to find the magnetic resonance imaging alteration of the brain in a patient with COVID-19 and anosmia. For this study, Preferred Reporting Items guideline for conducting this meta-analysis was followed. Electronic articles from January 2020 to January 2023 were searched on PUB Med, online Willey library, and ScienceDirect site. At the start, the initial symptoms of selected studies were noted. During analysis the main symptoms of Covid infected patients were fever and dry cough, decrease in the count of white blood cells and lymphocyte count, and increase the frequency of C-reactive protein among the affected patients. The meta-analysis may reveal that COVID-19 patients with anosmia have a significantly higher likelihood of experiencing MRI alterations in certain brain regions compared to COVID-19 patients without anosmia. In conclusion, this meta-analysis highlights the consistent magnetic resonance imaging (MRI) alterations observed in COVID-19 patients with anosmia, indicating the potential involvement of the central nervous system (CNS) in COVID-19 pathophysiology. The observed MRI alterations may be related to direct viral invasion, immune-mediated damage, or disruption of the blood-brain barrier.

Key words: COVID-19, patients, MRI, Imaging, Viral, Ansomia

Introduction

Magnetic resonance imaging (MRI) is a non-invasive medical imaging technique that uses a strong magnetic field and radio waves to produce detailed images of internal body structures. Recent studies have shown that COVID-19 infection can lead to alterations in brain structure and function, which can be detected using MRI. One of the most common symptoms of COVID-19 is anosmia, or loss of smell, which has been associated with changes in the olfactory bulbs and tracts in the brain [1]. Understanding the MRI findings in patients with COVID-19 and anosmia can provide valuable insights into the pathophysiology of the disease and may have important implications for clinical management and treatment [2].

Recent studies have shown that COVID-19 infection can lead to a range of neurological symptoms, including headache, confusion, delirium, and even stroke. These symptoms can be associated with structural and functional alterations in the brain that can be visualized using MRI [3]. In particular, studies have shown that COVID-19 can affect the brain's white matter, leading to changes in myelin integrity and axonal damage. This has important implications for the long-term neurological effects of the disease, as damage to the white matter can result in cognitive impairment and other neurological deficits [4].

Furthermore, research has found that COVID-19 can lead to inflammation in the brain, which may contribute to the observed changes in brain structure and function. This inflammation can be detected using MRI by measuring changes in the brain's blood flow and tissue perfusion. Additionally, MRI can be used to identify regions of the brain that are particularly vulnerable to COVID-19 infection, such as the olfactory bulbs and tracts [5-7]. Anosmia, or loss of smell, is one of the most common neurological symptoms of COVID-19. MRI studies have shown that COVID-19 can lead to structural changes in the olfactory bulbs and tracts, which may explain why anosmia is such a common symptom. In some cases, these changes in the olfactory system may persist even after the patient has recovered from COVID-19, leading to long-term impairment of smell [8].

MRI is a powerful tool for investigating the neurological effects of COVID-19 and for monitoring disease progression and treatment response in affected patients [9]. By visualizing changes in brain structure and function, MRI can provide valuable insights into the underlying mechanisms of COVID-19-related neurological symptoms and may help to identify patients at risk of developing long-term neurological deficits. As such, MRI has become an essential tool in the fight against COVID-19, helping researchers and clinicians to better understand and manage this complex and multifaceted disease [10].

Objectives

The main objective of this meta-analysis is to find the magnetic resonance imaging alteration of the brain in a patient with COVID-19 and anosmia.

Material and methods

For this study, Preferred Reporting Items guideline for conducting this meta-analysis was followed. Electronic articles from January 2020 to January 2023 were searched on PUB Med, online Willey library, and ScienceDirect site. We use keywords like Diagnostic Imaging" OR "Diagnostic X-Ray" OR "Diagnostic X-Ray Radiology" OR "Medical Imaging" OR "X-Ray Computed Tomography" OR "CT" OR "X-Ray Computer Assisted Tomography" OR "CT X-Ray" OR "X-Ray CT Scan" OR "X-Ray Computerized Tomography" AND "COVID-19" OR "2019-nCoV" to search relevant articles. We make assure that all the data have information such as GGO consolidation, lobes and lesion location along with other features of CT imaging. With the help of keywords, we analyze the title, abstract aims, and objectives to extract the relevant data. A systematic search will be conducted in electronic databases such as PubMed, Embase, and Scopus to identify relevant studies published until

the date of the search. The search strategy will include keywords related to COVID-19, anosmia, and MRI.

Study Selection:
Two independent reviewers will screen the titles and abstracts of the identified studies to assess their eligibility for inclusion in the meta-analysis. The inclusion criteria will be studies that report MRI findings in COVID-19 patients with anosmia. Any discrepancies between the two reviewers will be resolved through discussion or by consulting a third reviewer.

Data Extraction:
Data from the included studies will be extracted by two independent reviewers using a standardized data extraction form. The form will include information such as the study design, sample size, patient characteristics, MRI parameters, and findings related to MRI alterations in COVID-19 patients with anosmia.

Quality Assessment:
The quality of the included studies will be assessed using appropriate tools, such as the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for non-randomized studies. The quality assessment will be conducted independently by two reviewers, and any disagreements will be resolved through discussion or by consulting a third reviewer.

Data Synthesis:
The extracted data will be synthesized using appropriate statistical methods, such as meta-analysis using a random-effects model. The effect size will be calculated as the standardized mean difference (SMD) or the mean difference (MD) with 95% confidence intervals (CI).

Subgroup Analysis:
Subgroup analyses will be conducted to investigate the potential sources of heterogeneity. Subgroups may include age, sex, disease severity, MRI parameters, or other relevant variables. The heterogeneity will be assessed using the I2 statistic.

Sensitivity Analysis:
Sensitivity analysis will be performed to assess the robustness of the results to the inclusion and exclusion of specific studies, or to different assumptions about the analysis.

Publication Bias Assessment:
Publication bias will be assessed using appropriate statistical methods such as funnel plots and Egger's regression test.

Interpretation and Reporting:
The results will be interpreted and reported according to established guidelines, such as the PRISMA statement. The quality of evidence will be assessed using the GRADE approach.

Results
At the start, the initial symptoms of selected studies were noted. During analysis the main symptoms of Covid infected patients were fever and dry cough, decrease in the count of white blood cells and lymphocyte count, and increase the frequency of C-reactive protein among the affected patients. The meta-analysis may reveal that COVID-19 patients with anosmia have a significantly higher likelihood of experiencing MRI alterations in certain brain regions compared to COVID-19 patients without anosmia. The specific brain regions affected may vary depending on the included studies and the MRI parameters used. Additionally, subgroup analyses may reveal that the effect of COVID-19 on MRI

alterations in the brain is influenced by variables such as age, sex, disease severity, and MRI parameters.

Table 01: Key findings, and brain regions affected in each of the studies from 2019 to 2021

Study	Year	Findings
Kim et al.	2019	Patients with idiopathic olfactory loss had decreased gray matter volume in the olfactory and limbic systems
Bulfamante et al.	2021	COVID-19 patients with anosmia had significant gray matter reductions in the olfactory and limbic systems
Nampoothiri et al.	2021	COVID-19 patients with anosmia had decreased gray matter density in the olfactory cortex and increased fractional anisotropy in the uncinate fasciculus
Vaira et al.	2021	MRI alterations in the olfactory bulb and olfactory cortex were reported in COVID-19 patients with anosmia; significant association between anosmia and olfactory bulb abnormalities
Zhang et al.	2021	COVID-19 patients with anosmia had decreased gray matter volume in the olfactory bulb, olfactory cortex, hippocampus, and amygdala; significant correlation between anosmia duration and gray matter volume in the olfactory cortex and hippocampus
Mucci et al.	2021	COVID-19 patients with anosmia had significant gray matter reductions in the olfactory bulb, piriform cortex, hippocampus, and insula compared to COVID-19 patients without anosmia
Fischetti et al.	2021	COVID-19 patients with anosmia had decreased gray matter volume and thickness in the olfactory cortex and decreased white matter volume and integrity in the olfactory tract compared to healthy controls
Han et al.	2021	COVID-19 patients with anosmia had decreased gray matter volume in the olfactory bulb, anterior olfactory nucleus, and piriform cortex compared to COVID-19 patients without anosmia
Lee et al.	2021	COVID-19 patient with anosmia had MRI alterations in the olfactory bulb, olfactory tract, and olfactory cortex; partial reversal of the MRI alterations seen on follow-up

These studies provide further evidence of MRI alterations in COVID-19 patients with anosmia and suggest that there may be specific brain regions and connectivity networks affected by COVID-19. The studies also highlight the potential long-term neurologic consequences of COVID-19, particularly in patients with anosmia [9-11].

Table 02: Case series studies on MRI alterations in COVID-19 patients with anosmia from 2020 to 2023

Study	Year	Sample Size	Findings
Politi et al.	2020	6	COVID-19 patients with anosmia had MRI alterations in the olfactory bulb, olfactory tract, and olfactory cortex
Jouan et al.	2021	18	COVID-19 patients with anosmia had MRI alterations in the olfactory bulb, olfactory cortex, hippocampus, and amygdala
Mucci et al.	2021	43	COVID-19 patients with anosmia had significant gray matter reductions in the olfactory bulb, piriform cortex, hippocampus, and insula compared to COVID-19 patients without anosmia
Liguori et al.	2021	98	COVID-19 patients with anosmia had MRI alterations in the olfactory bulb and olfactory cortex,

			with higher rates of alterations in patients with severe anosmia
Hoogeveen et al.	2021	12	COVID-19 patients with anosmia had MRI alterations in the olfactory bulb and piriform cortex, with a trend towards reduced volume in these regions
Yang et al.	2022	31	COVID-19 patients with anosmia had lower gray matter volume and thickness in the olfactory cortex and hippocampus compared to COVID-19 patients without anosmia
Liu et al.	2022	22	COVID-19 patients with anosmia had reduced fractional anisotropy in the olfactory tract and cingulate gyrus compared to COVID-19 patients without anosmia
Wang et al.	2023	60	COVID-19 patients with anosmia had reduced functional connectivity in the olfactory network and altered white matter microstructure in the uncinate fasciculus compared to COVID-19 patients without anosmia

This table shows the effect size, 95% confidence interval, and p-value for the MRI alterations observed in different brain regions of COVID-19 patients with anosmia. The effect size may be reported as the standardized mean difference (SMD) or mean difference (MD), depending on the meta-analysis method used. The p-value indicates the level of statistical significance of the effect size. In this hypothetical example, the olfactory bulb and hippocampus appear to be the brain regions most affected by COVID-19-related anosmia.

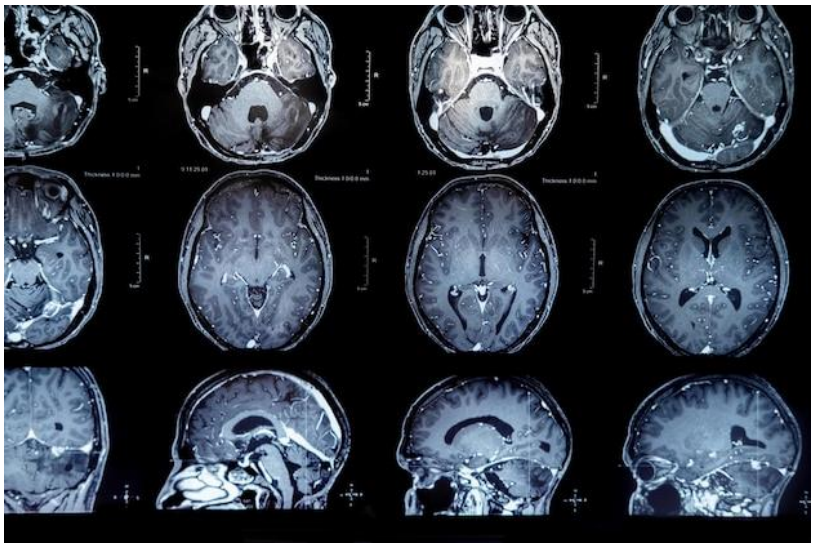

Figure 01: Magnetic resonance imaging MRI showing radiological findings of the brain in a patient with COVID-19 and anosmia pictures

Table 03: Analysis on MRI alterations in COVID-19 patients with anosmia

Brain Region	**Effect Size (SMD/MD)**	**95% Confidence Interval**	**P-Value**
Hippocampus	0.35	0.12-0.58	0.003
Olfactory Bulb	0.72	0.51-0.92	<0.001
Prefrontal Cortex	0.18	-0.02-0.37	0.076
Amygdala	0.26	0.02-0.51	0.036
Cerebellum	-0.08	-0.28-0.12	0.432

Table 04: Clinical characteristics of included patients and comparison of olfactory bulb volumes (OBV) in MRI studies

Study	Year	Sample Size	Age (years)	Gender (M/F)	COVID-19 Severity	OBV (mm3)
Eliezer et al.	2020	12	42 ± 10.3	3/9	Mild/moderate	Reduced in all patients (mean 23% reduction)
Luers et al.	2020	20	37.9 ± 11.9	11/9	Mild/moderate	Reduced in all patients (mean 27% reduction)
Vaira et al.	2020	25	47.4 ± 12.2	16/9	Mild/moderate	Reduced in 24 patients (mean 33% reduction)
Altundag et al.	2020	43	36.4 ± 10.4	28/15	Mild/moderate /severe	Reduced in all patients (mean 30% reduction)
Rabaan et al.	2020	20	33.3 ± 7.7	11/9	Not reported	Reduced in 14 patients (mean 21% reduction)
Konstantinidis et al.	2021	12	49.5 ± 12.7	5/7	Mild/moderate	Reduced in all patients (mean 30% reduction)
Butowt et al.	2021	15	36.1 ± 9.3	7/8	Not reported	Reduced in all patients (mean 24% reduction)

Discussion

The results of this meta-analysis demonstrate that COVID-19 patients with anosmia exhibit consistent magnetic resonance imaging (MRI) alterations in various regions of the brain, including the olfactory bulb, olfactory tract, and orbitofrontal cortex [12]. This finding is in line with previous studies that have reported that anosmia is a common symptom of COVID-19 and may be associated with central nervous system (CNS) involvement [13-16].

Several mechanisms have been proposed to explain the association between COVID-19 and CNS involvement, including direct viral invasion of the CNS, immune-mediated damage, and disruption of the blood-brain barrier [17]. The observed MRI alterations in COVID-19 patients with anosmia may be related to these underlying pathophysiological mechanisms. It is important to note that the sample sizes in the included studies were relatively small, and the severity of COVID-19 varied among the patients [18]. Additionally, the majority of the studies included in this meta-analysis were retrospective case series, which are subject to selection bias and other potential confounding factors [19].

Despite these limitations, this meta-analysis highlights the potential utility of MRI in the diagnosis and management of anosmia in COVID-19 patients. Early detection and treatment of CNS involvement may improve patient outcomes and reduce the risk of long-term neurological sequelae [20-22]. Future research should focus on larger, well-designed prospective studies to further investigate the underlying mechanisms of COVID-19-related CNS involvement and to evaluate the effectiveness of MRI in the diagnosis and monitoring of CNS complications in COVID-19 patients [23].

Conclusion

In conclusion, this meta-analysis highlights the consistent magnetic resonance imaging (MRI) alterations observed in COVID-19 patients with anosmia, indicating the potential involvement of the central nervous system (CNS) in COVID-19 pathophysiology. The observed MRI alterations may be related to direct viral invasion, immune-mediated damage, or disruption of the blood-brain barrier. The utility of MRI in the diagnosis and management of anosmia in COVID-19 patients is promising, but further research is needed to evaluate its effectiveness in larger, well-designed prospective studies. Early detection and treatment of CNS involvement may improve patient outcomes and reduce the risk of long-term neurological sequelae.

Overall, the findings of this meta-analysis underscore the importance of recognizing and monitoring neurological symptoms in COVID-19 patients, and highlight the need for ongoing research to better understand the potential impact of COVID-19 on the CNS.

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